Replaced by Art. 34

CLAIMS

1. A method for preparing a steroidal carbothioic acid or a salt thereof, said method comprises:

A) reacting a steroidal carboxylic acid or a salt thereof with a coupling agent alone or in conjunction with a coupling enhancer; and

B) reacting the product of step A) with a nucleophilic agent comprising a sulfur atom.

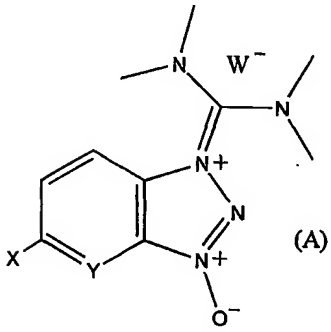
2. A method according to claim 1 in which the coupling agent is selected from the group consisting of carbodiimide derivatives represented by the following formula:

$R_a—N=C=N—R_b$

wherein R_a and R_b are the same or different, and each represent an aliphatic, heteroaliphatic, carbocyclic or a heterocyclic group [all said groups are optionally substituted]; preferably the coupling agent is 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC); and more preferably the hydrochloride salt of EDC.

3. A method according to claim 1, in which the coupling agent is selected from the group consisting of:

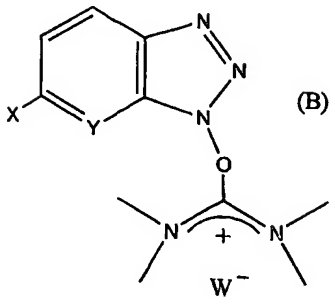
A) derivatives of guanidinium N-oxide salts (N-methyl methanaminium salts) of a unsaturated 5-membered heterocyclic ring fused to an optionally substituted aryl, heteroaryl, benzene- or pyridine ring, (such as compounds of formula (A)),



(A)

X = H, F, Cl, Br and Y = CH, N, O, S, $W^- = PF_6, BF_4, SbCl_6$;

B) derivatives of uronium salts (O-hydronated ureas) of a unsaturated 5-membered heterocyclic ring fused to a optionally substituted aryl, heteroaryl, benzene- or pyridine ring, (such as compounds of formula (B)),

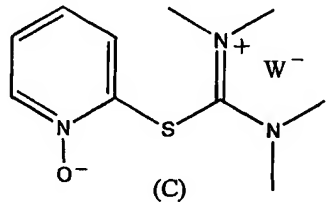


(B)

X = H, F, Cl, Br and Y = CH, N, O, S, W^- = PF_6, BF_4, $SbCl_6$;

and;

C) derivatives of thiouronium salts (such as compounds of formula (C), preferably as the tetrafluoroborate salt),

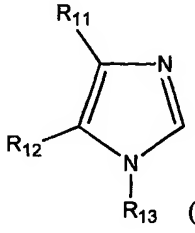


(C)

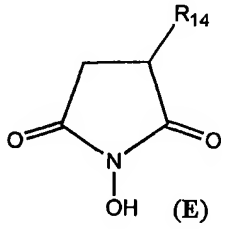
W^- = BF_4, PF_6, $SbCl_6$

4. A method according to any of the preceding claims, in which the coupling enhancer is selected from the group consisting of:

A) a heterocyclic ring containing one or two nitrogen atoms, said ring being optionally substituted; such as a compound of formula (D) or formula (E),



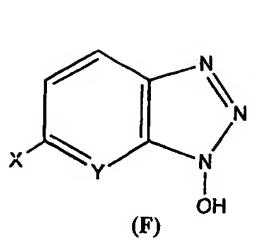
(D)



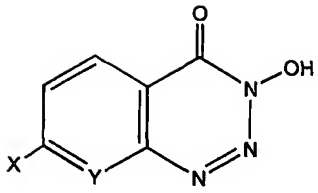
(E)

wherein R_{11} and R_{12} can be the same or different, and each represent a hydrogen atom or a cyano group; R_{13} represent a hydrogen atom or an alkyl group; and R_{14} represent a hydrogen atom or a salt of a sulfonic acid such as sodium sulfonate [-S(=O)(=O)-O^- Na^+]; and

B) an unsaturated 5-6 membered heterocyclic ring fused to an aromatic- or heteroaromatic ring in which the said heterocyclic ring contains three nitrogen atoms, said rings being optionally substituted, such as a compound of formulas (F), (G)



(F)



(G)

X = H, F, Cl, Br and Y = CH, N, O, S

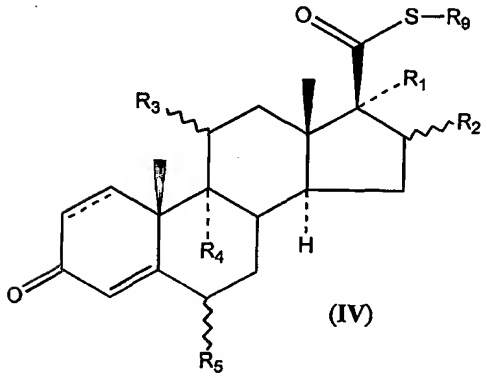
preferably 6-chloro-hydroxybenzotriasole (6-Cl-HOBt), 7-aza-hydroxybenzotriasole (HOAt), or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (Dbht-OH).

5. A method according to any of the preceding claims, where the nucleophilic agent comprising a sulfur atom is selected from the group comprising:

- compounds of formula $[M]^+[SH]^-$ wherein M is a metal such as Li, Na or K; or $[M]^{2+}[S]^{2-}$ wherein M is a metal such as Ca or Mg, the said sulfide salts being optionally hydrated (such as sodium hydrosulfide hydrate); and
- an *in situ* generated sulfide salt or a hydrated sulfide salt.

6. The method of any of the preceding claims, wherein the nucleophilic agent is dissolved in a suitable solvent prior to addition to the reaction mixture, or wherein the nucleophilic agent is added in the form of a solid salt or as a solution of the salt in water and/or an organic solvent or a combination thereof.

7. A method according to any of the preceding claims for preparing a steroidal carbothioic acid of formula (IV) or a salt thereof

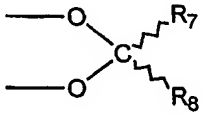


(IV)

Wherein the symbol ==== in the 1,2-position represent a single or a carbon-carbon double bond;

R_1 represents a hydrogen atom, a hydroxy- or an alkoxy group (such as an optionally substituted C_{1-6} alkoxy) in the α-configuration, a group -O-C(=O)-R_6, where R_6 is an alkyl group (such as optionally substituted C_{1-6} alkyl) or an optionally substituted 5-6 membered heterocyclic ring containing either oxygen, nitrogen or sulfur as ring hetero atom (such as a furanyl-, pyrrolyl- or a thiophenyl group);

R_2 represents a hydrogen atom, a hydroxy group, an alkoxy group (such as an optionally substituted C_{1-6} alkoxy) in the α-configuration, an alkyl group (such as an optionally substituted C_{1-6} alkyl) which may be in either the α- or β-configuration, an alkylene group (such as an optionally substituted C_{1-6} alkylene having the two free valencies on the same carbon atom, preferably methylene) [the alkylene group bound to the steroid nucleus via a double bond] or R_1 and R_2 together represent



where R_7 and R_8 are the same or different and each represent a hydrogen atom or an alkyl group (such as an optionally substituted C_{1-6} alkyl);

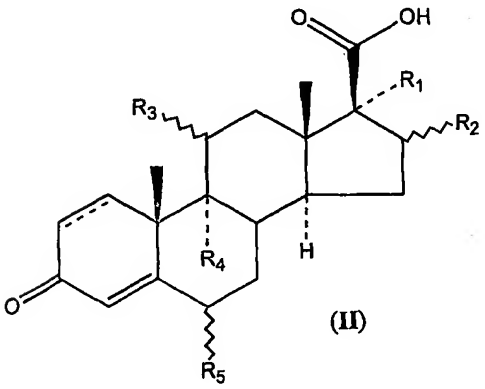
R_3 represent a hydrogen atom, hydroxy- or a protected hydroxy group in either the α- or β-configuration or an oxo group (in which case the bond between R_3 and the steroid nucleus is a double bond);

R_4 represents a hydrogen- or a halogen atom or R_3 and R_4 together represent a carbon-carbon bond or an epoxy group in the β-configuration; and

R_5 represents a hydrogen- or a halogen atom in either the α- or β-configuration;

R_9 represents a hydrogen atom or R_9 represent a metal ion [eg. the moiety -S-R_9 represents a group of the formula $[-S]^-[M]^+$ wherein M is a metal such as Li, Na or K]; the method comprising;

A) reacting a steroidal carboxylic acid of formula (II) or a salt thereof



(II)

in which the substituents of formula (II) have the above defined meaning with a coupling agent alone or in conjunction with an coupling enhancer, followed by the reaction with a nucleophilic agent comprising a sulfur atom; and optionally

B) reacting the product from step A) with an acid.

8. The method of any of the preceding claims, wherein i)

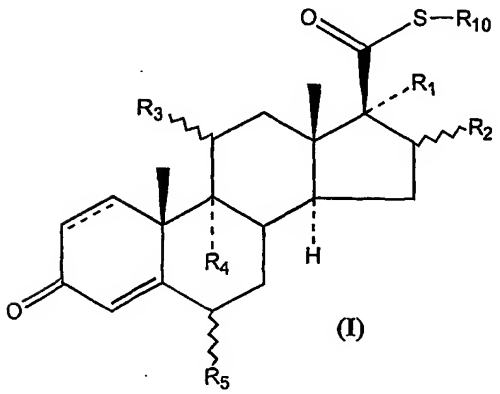
- the coupling agent is added before the coupling enhancer, or
- the coupling enhancer is added before the coupling agent, and/or wherein ii)
- the steroidal carboxylic acid is added to a mixture of the coupling agent and the coupling enhancer, or wherein
- a mixture of the coupling agent and the coupling enhancer is added to a steroidal carboxylic acid, or wherein
- the steroidal carboxylic acid is added to a mixture of the coupling agent and the coupling enhancer in a polar aprotic solvent, preferably DMF or DMA, at elevated temperature.

9. A method for preparing a steroidal carbothioate (i.e. the carbothioic ester of the steroid), or a salt thereof, the method comprising;

reacting a steroidal carbothioic acid or a salt thereof, which is prepared as defined in any of the preceding claims, with an electrophilic agent.

10. A method according to claim 9, in which the electrophilic agent is selected from the group consisting of: C_{1-6} di- or trihaloalkanes, preferably a trihalo- or a dihalomethane, such as chlorobromomethane or bromofluoromethane.

11. A method according to claim 9 or 10 for preparing a steroidal carbothioate of formula (I)

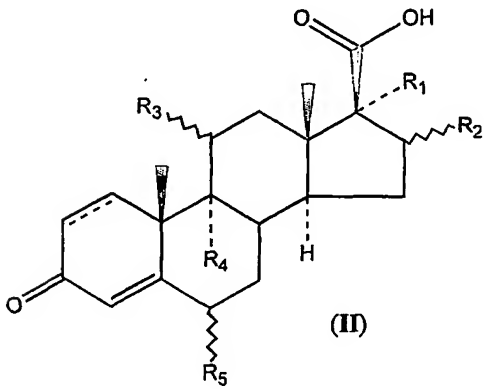


(I)

wherein R_1, R_2, R_3, R_4, and R_5 are defined as in claim 7; and

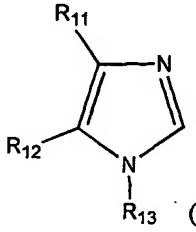
R_{10} represents a C_{1-6} haloalkyl or an optionally substituted heterocyclic ring, the method comprising:

A) reacting a steroidal carboxylic acid of formula (II)

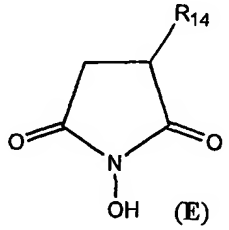


(II)

with a coupling agent and a coupling enhancer [such as a compound of formula (D) or formula (E)]



(D)



(E)

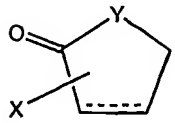
wherein R_{11} and R_{12} independently represent a hydrogen atom or a cyano group (C≡N);

R_{13} represent a hydrogen atom or an alkyl group; and

R_{14} represent a hydrogen atom or a moiety of a sulfonic acid, such as sodium sulfonate (eg. the group $-S(=O)(=O)-O^-Na^+$)];

B) reacting the product from step A) with a nucleophilic agent comprising sulfur; and

C) reacting the product from step B) with an electrophilic agent [such as a C_{1-6} di- or trihaloalkane, preferably a trihalo- or a dihalomethane such as chlorofluoromethane or bromofluoromethane] or a compound of the following formula;



wherein X=H, F, Cl, Br and; Y=CH_2, NH, O, S, preferably X=Cl and Y=O.

12. The method of claim 11, wherein the coupling enhancer is selected from the group consisting of: NMI (N-methylimidazole); DCI (4,5-dicyanoimidazole); NHS (N-hydroxysuccinimide); and sulfo-NHS (N-hydroxysulfosuccinimide).

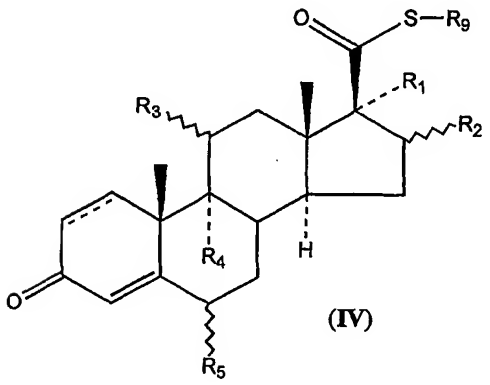
13. The method of any of the claims 11-12, wherein step C) constitutes the *in situ* reaction of the product from step B) with bromofluoromethane to form a compound of formula (I) wherein R_{10} is a fluoromethyl group, such as fluticasone propionate.

14. The method according to any of the preceding claims, in which

- at least two subsequent steps are performed *in situ*, i.e. without any change or removal of solvents, or isolation of the individual intermediates; and/or
- the method is conducted as a continuous method; and/or
- step A), B) and optionally step C) are conducted as a one-pot synthesis without solvent changes and/or are performed at room or elevated temperature.

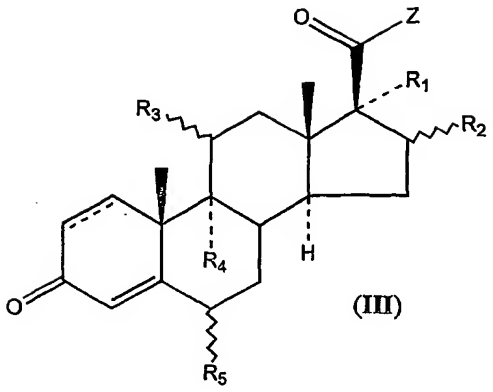
15. The method of any of the claims 9-14, wherein an androstane 17β-carboxylic acid is converted to an androstane 17β-carbothioate.

16. The method of any of the preceding claims, wherein step B) provides an alkali metal salt of the thioic acid, such as a compound of formula (IV), in which the moiety -S-R_9 represent a group of the formula $[-S]^-[M]^+$ wherein M is a metal such as Li, Na or K e.g. $-S^-Na^+$, and the other substituents have the same meaning as defined in claim 7.



(IV)

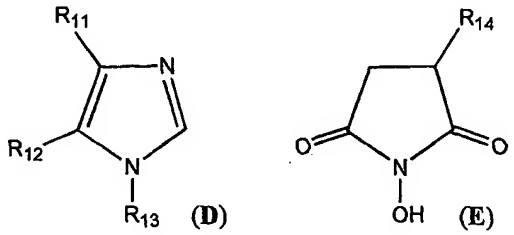
17. A compound of the formula (III) and salts and solvates thereof



(III)

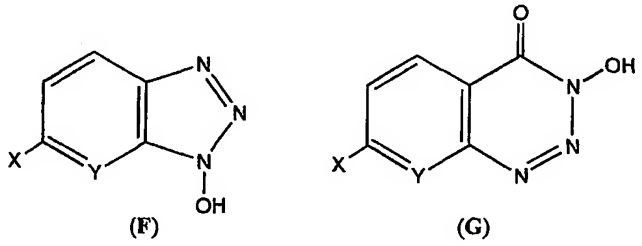
wherein R_1, R_2, R_3, R_4, and R_5 are defined as in claim 7; and

Z represent the structural moiety resulting from the reaction between the steroidal carboxylic acid of formula (II) and a coupling agent (preferably EDC), followed by a coupling enhancer as defined in claim 4, such as a compound selected from the group consisting of the compounds of formulas (D); (E); (F); and (G):



(D) (E)

wherein R_{11} and R_{12} independently represent a hydrogen atom or a cyano group; R_{13} represent a hydrogen atom or a methyl group; and R_{14} represent a hydrogen atom or a moiety of a sulfonic acid, such as sodium sulfonate [ie. the group $-S(=O)(=O)-O^- Na^+$],



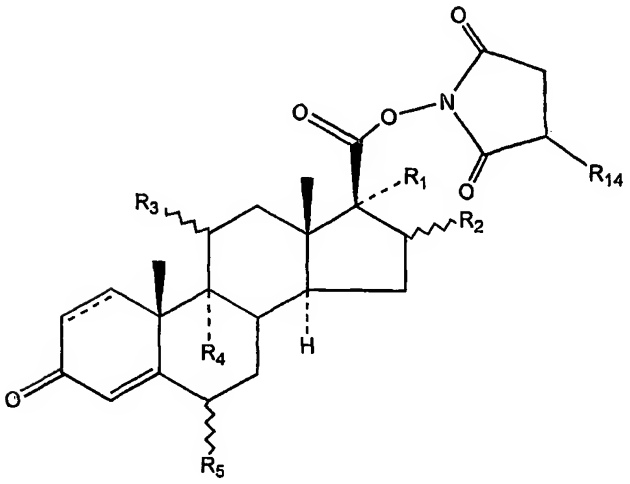
(F) (G)

X = H, F, Cl, Br and Y = CH, N, O, S

with the proviso that 1-[(9alpha-fluoro-11beta-hydroxy-16beta-methyl-3-oxo-17alpha-propionyloxyandrosta-1,4-dien-17beta-yl)carbonyl]imidazole is disclaimed.

18. The compound of claim 17, wherein at least one of R_{11} and R_{12} is a cyano group (C≡N), and/or R_{13} is a hydrogen atom, and/or formula (D) is NMI (N-methylimidazole) or DCI (4,5-dicyano-imidazole), and/or formula (E) is NHS (N-hydroxysuccinimide) or sulfo-NHS (N-hydroxysulfo-succinimide).

19. The compound having the formula:



in which the substituents have the same meaning as defined in claim 17, and salts and solvates thereof.

20. A composition comprising a compound as defined in any of claims 17-19.

21. Use of a compound of any of the claims 17-19 as an intermediate in a method for preparing a steroidal carbothioate or a steroidal carbothioic acid, such as in a method for preparing fluticasone propionate.

22. Use according to claim 21, in which the method comprises reaction with a nucleophilic agent comprising a sulfur atom and/or comprises reaction with an electrophilic agent.